Chapter 14
Liver Cancer

A1a. Establish liver cancer serum and tissue bank. Serum banks of patients with early hepatocellular carcinoma (HCC) and liver disease controls are being established through the NCI-supported Early Disease Recognition Network (EDRN) and through the HALT-C trial. (10%)

A1b. Establish means of active surveillance of HCC in the United States. Discussions of creating a prospective database on HCC cases have been held between the NCI and NIDDK. Databases have been initiated by the American Society for Clinical Oncology and other academic hepatology groups. (0%)

A2a. Identify potential biomarkers for early HCC. Targeted proteomics has identified Gp73 as a promising marker of HCC, the role of which is being evaluated (Block TM. *PNAS* 2005;102:779). (10%)

A2b. Define the molecular signatures and heterogeneity of HCC and determine how they correlate with clinical features. Intramural NCI investigators have described signature gene expression microarray patterns associated with HCC that correlate with survival (Lee JS *Nat Genetics* 2004;36:1306), while other groups have found associations between gene expression patterns and HCC stage (Nam SW. *Hepatology* 2005;42:809). (10%)

A3. Develop functional imaging techniques that can distinguish HCC from benign lesions. The NCI, NIDDK, NIBIB and NIAAA have jointly published a PA on "Etiology, Prevention, and Treatment of Hepatocellular Carcinoma" (PA-05-137/138) that encourages research on HCC, a major focus of which is functional imaging of tumors. (0%)

B1a. Demonstrate the relative efficacy, safety, and benefits of local ablative therapies for HCC. The PA listed above (PA-05-137/138) encourages studies of therapy of HCC. Impressive results have been obtained with percutaneous image-guided radiofrequency ablation (Lencioni R. *Radiology* 2005;234:961). Prospective controlled trials are warranted. (0%)

B1b. Develop standardized terms and nomenclature for diagnosis, staging, and grading of HCC. The AASLD, in collaboration with the NIH, is organizing a research workshop on development of standardization of terminology and staging systems for HCC which is scheduled for December 2006. Comparisons of current staging systems have been published (Marrero JA. *Hepatology* 2005;41:707). (0%)

B2a. Validate reliability of biomarkers for early detection of HCC. Analyses of several biomarkers for HCC (e.g., DCP and AFP-L3) are underway as a part of the HALT-C trial, and the EDRN is sponsoring a validation study of DCP. Serum samples from patients in the HALT-C trial are being stored in a repository and will provide an outstanding resource to evaluate new markers for detection of HCC before it is clinically apparent. (10%)

B2b. Identify risk factors for HCC associated with NASH. Epidemiologic studies have clearly linked obesity and diabetes with increased risk of HCC (El Serag HB. *Gastroenterology* 2005;126:460), and prospective studies of NASH are incorporating screening tests for HCC in the NIH-funded NASH Clinical Research Network. (10%)

B3. Identify target for potential therapy of HCC from molecular studies on human tissue and/or animal models. Several potential cellular pathways have been identified in HCC that might serve as targets for non-cytolytic therapy. Such studies are encouraged in PA-05-137. (0%)

C1. Demonstrate an effective strategy for prevention of HCC in high-risk populations. The HALT-C trial and a similar study supported by industry (Schering, Epic-3) are evaluating the role of long-term, low dose peginterferon as a means of decreasing disease progression and development of HCC in patients with chronic hepatitis C and advanced fibrosis or cirrhosis. Studies of chemoprevention of HCC in aflatoxin-endemic areas are underway and focus upon oltipaz and chlorphyllin. (0%)

C2. Define the cellular and molecular pathways that lead to hepatocarcino-genesis. This is the topic of many current investigator-initiated research program grants and is a research area highlighted in PA-05-137. Pathways recently identified in association with HCC include those of frizzled-7/beta catenin (Merle P. *J Hepatol* 2005;43:854), platelet-derived growth factor C (Campbell JS. *PNAS* 2005; 102:3389), and hedgehog (Sicklick JK. *Carcinogenesis* 2005; In press). (0%)

C3. Based upon molecular analyses, develop effective, noncytotoxic therapy for HCC. Noncytotoxic therapies of HCC targeted at cellular and molecular pathways await demonstration of the importance of specific pathways in hepatic carcinogenesis. (0%)

Figure 16. Estimated Progress on Liver Cancer Research Goals, 2005 (Year 1)